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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/971,929	10/09/2001	Naoyuki Takano	2185-0577P	2971

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BIRCH, STEWART, KOLASCH & BIRCH, LLP
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Falls Church, VA 22040-0747

EXAMINER

GUDIBANDE, SATYANARAYAN R

ART UNIT	PAPER NUMBER
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1654

MAIL DATE	DELIVERY MODE
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01/08/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/971,929

Applicant(s)

TAKANO ET AL.

Examiner

Satyanarayana R. Gudibande

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 7, 9-14 and 16-21 is/are pending in the application.
- 4a) Of the above claim(s) 3-5, 7, 16 and 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 9-14, 17 and 19-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☒ Other: Notice of Seq. Compliance

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of species chitosan trisaccharide and diethylenetriaminepentaacetic acid in the reply filed on 9/26/06 was acknowledged in office action dated 10/30/06.

Examiner searched the elected species chitosan trisaccharide and diethylenetriaminepentaacetic acid found them free of art. Examiner extended the search and found art on serum albumin and diethylenetriaminepentaacetic acid.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/6/07 has been entered.

Applicant's amendment to claims 1 and 19-21 in the response filed on 12/6/07 has been acknowledged.

Claims 1-5, 7, 9-14 and 16-21 are pending.

Claims 6, 8 and 15 have been canceled.

Claims 3-5, 7, 16 and 18 are withdrawn from further consideration as being drawn to non-elected species.

Claims 1, 2, 9-14, 17 and 19-21 are examined on the merit.

Allowable Subject Matter

Claim 19 contain allowable subject matter, i.e., claim is drawn to the elected species chitosan trisaccharide that has been found to be free of art, but contains other species chitosan tetra- to deca-saccharide.

Any objections and rejections made in the previous office action dated 8/6/07 and not specifically mentioned here are considered withdrawn.

Specification

Specification contains peptide sequences (page 2, line 25) that require SEQ ID NO. Applicants are required to submit a paper copy of the sequence listing and a copy in the Computer Reader Format (CRF) of the same.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,2, 9-14, 17 and 19-21 remain rejected under 35 U.S.C. 102(b) as being anticipated by Paik, et al., J. Nucl. Med. 1983, 1158-1163. In the instant application, applicants claim a process of producing an amide bond that comprises of reacting a compound having an amino group with a polyaminopolycarboxylic acid anhydride in the presence of the polyaminopolycarboxylic acid.

Note: Applicant's arguments have been addressed at the end of the reiteration of the rejection.

In the instant application, applicants claim a process of producing an amide bond that comprises of reacting a compound having an amino group with a polyaminopolycarboxylic acid anhydride in the presence of the polyaminopolycarboxylic acid.

Paik, et al., teaches such a method of amide formation. The reference teaches the preparation of DTPA coupled serum albumin antibody. In the process, Paik, et al., affinity-purified antibody (300 μ g, 2.0 nmol) was dissolved in 1 ml of 0.1M buffer solution (Hepes buffer at pH 7, phosphate at pH 7, borate at pH 8.6, or bicarbonate at pH 8.2) in a 2.5-ml vial. To the antibody solution was added solid cyclic DTPA anhydride (page 1159, column 2, paragraph 1). However, during the IR (infrared spectroscopy) analysis of the DTPA anhydride, Paik, et al., the IR spectrum showed absorption bands at 1825 and 1780 cm^{-1} , characteristic stretching vibrations for the **anhydride carbonyl group**. The IR spectrum also showed an absorption at

1640 cm^{-1} indicating the presence of a **carboxylate group**. The claim limitation that the presence of both polyaminopolycarboxylic acid anhydride and the presence of the polyaminopolycarboxylic acid in the reaction mixture is met by the fact that the anhydride used in the preparation was a mixture of the anhydride and the free acid as shown by the IR analysis. Therefore, this meets claim limitations of claims 1 and 21. Also, during the DTPA conjugation reaction, the reaction reduced the pH of buffer solution to 4. Due to the hydrolysis of the anhydride that produced four acetic acid molecules (page 1161, column 1, paragraph 1) further affirming the presence of free polyaminocarboxylic acid in the reaction mixture. The reaction was carried out in bicarbonate buffer, pH, 8.2 as mentioned above and hence in basic condition that meets one of the limitations of claim 21.

Response to Arguments

Applicants argue that not all instantly claimed features are disclosed in the cited reference of Paik, et al., and polyaminopolycarboxylic acid is not even disclosed in Paik et al. Applicants point out that the DTPA anhydride molecule has two anhydride moieties and acetic acid residue shows absorption bands characteristic of anhydride carboxyl and carboxylate. The cited reference does not teach that there is DTPA which has five free acetic acid residues and therefore the presence of single acetic acid residue on a DTPA anhydride residue does not meet the requirement of the instant claim.

Applicants further argue that hydrolysis of the anhydride reduced the pH of the buffer solution and merely teaches the desired acylation of one anhydride group resulted in the formation of an acetic acid residue but it does not mention that polyaminopolycarboxylic acid

per se was present or added to the reaction. Hence, the reaction of Paik, was not conducted in the presence of the polyaminopolycarboxylic acid.

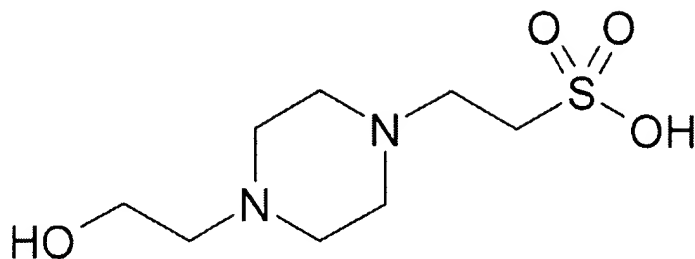
Applicants further argue that the instantly claimed process shows superior results compared to the comparative example of the present specification where the polyaminopolycarboxylic acid was not used in the reaction. Applicants also acknowledge that the statute under the current rejection is not overcome by unexpected result and the evidence of unexpected results reside in the present specification and it is improper not to consider such evidence of patentability for the instant invention.

Applicants have amended the claims to include the limitations such as, "the polyaminopolycarboxylic acid anhydride is added to a mixture of the compound having an amino group and the polyaminopolycarboxylic acid, or the compound having an amino group and the polyaminopolycarboxylic acid anhydride are added to the polyaminopolycarboxylic acid," and the cited reference clearly fails to teach or suggest such an embodiment. Applicants also state that the presence of DTPA in the reaction mixture is due to hydrolysis of DTPA anhydride present due to its *in situ* formation and the claims as recited require that the polyaminopolycarboxylic acid is added to the reaction mixture.

Applicant's arguments filed 12/6/07 have been fully considered but they are not persuasive.

Applicant's argument that "polyaminopolycarboxylic acid is not even disclosed in Paik et al" is not true. The reference discloses the compound DTPA in column 1, page 1159, paragraph 1, under the section "preparation of cyclic DTPA anhydride". It is true that the DTPA anhydride

of the cite reference has one acetic acid moiety and four other acetic acid moieties are involved in the dianhydride formation. However, applicant's claims are drawn to "a process for producing an amide compound, which **comprises** of....." that does not preclude the presence other ingredients. Also, the claims are drawn to "[i]n the presence of the polyaminopolycarboxylic acid and wherein the polyaminopolycarboxylic acid anhydride is added to a mixture of the compound having an amino group and the polyaminopolycarboxylic acid, or the compound having an amino group and the polyaminopolycarboxylic acid anhydride are added to the polyaminopolycarboxylic acid". The claim as recited does not imply that the polyaminopolycarboxylic anhydride is derived from the same polyaminopolycarboxylic acid. The specification on page 6, lines 4 and 6 discloses that "a polyaminopolycarboxylic acid corresponding to the polyaminopolycarboxylic acid anhydride is usually used". This clearly states that the a polyaminopolycarboxylic acid corresponding to polyaminopolycarboxylic acid anhydride is always used. Hence other polyamino and polycarboxylic acid compounds could be used in the practice of the instant invention. Also, this would imply that the polyaminopolycarboxylic acid may not be a single moiety and the invention could be practiced in the presence of other amino and carboxylic compounds. In such a situation, the reference of Paik teaches the acylation reaction in the presence of a 0.1 M buffer mixture of hepes, phosphonate, borate and bicarbonate. The hepes buffer is prepared using 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, the structure of which appears below,



and the bicarbonate buffer has the carboxyl moiety. And hence the reference of Paik anticipates the instant invention. Over and above the presence of the IR band in the preparation of cyclic DTPA anhydride may not be entirely due the presence of single acetic acid moiety as the anhydrides are notoriously unstable compounds. Even at 99.9% pure, the presence of 0.1% impurity in the form monoanhydride and the DTPA there is considerable number of polyaminopolycarboxylic acid molecules present in the DTPA anhydride and hence the addition of the anhydride to the amine compound always accompanies with the unreacted DTPA or hydrolyzed anhydride compounds.

With respect to applicant's comment about the evidence of unexpected result the addition of DTPA or polyaminopolycarboxylic acid, it should be noted that in the following reaction in the presence of aqueous buffer,



wherein R-NH₂ is the amine that is modified via acylation, the addition of DTPA to the reaction would deter the rate of hydrolysis reaction of the DTPA anhydride and favor the formation of the R-DTPA according to the well known Le Chatelier's principle. The information on the website "http://www.800mainstreet.com/7/0007-008-le_chatelier.html" provides credence to the above observation. The information available clearly states that "adding reactants by increasing the concentration of the product to the reaction favors the reactants" (see the summary section), and

in the instant case slows the hydrolysis of the anhydride and hence assists the formation of the desired product. Hence, even though, there is evidence in the instant case that addition of polyaminopolycarboxylic acid result in unexpected results, it is obvious to observe such improvements in the formation of desired products according to the well known Le Chatelier's hypothesis. The cited website reference with respect to Le Chatelier's principle is post dated to the effective filing date of the application. However, Le Chatelier's principle or hypothesis is scientific fact. See MPEP section 2124 under, 'Exception to the Rule That the Critical Reference Date Must Precede the Filing Date'. In certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. In re Wilson, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism.

Therefore, the cited reference of Paik, et al., anticipates instant invention and hence maintained.

Conclusion

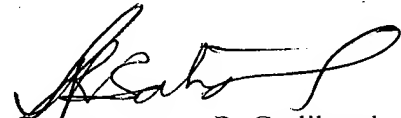
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Satyanarayana R. Gudibande, Ph.D.
Art Unit 1654



ANISH GUPTA
PRIMARY EXAMINER

NOTICE TO COMPLY

Application/Control No.

09/971,929

Examiner

Satyanarayana R. Gudibande

Applicant(s)

TAKANO ET AL.

Art Unit

1654

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other: ***

Applicant Must Provide:

- ☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923

For CRF Submission Help, call (703) 308-4212 or 308-2923

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